

4-Aminophthalic Acid and Some of Its Derivatives

DISSERTATION

SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIRE-
MENTS FOR THE DEGREE OF DOCTOR OF PHILOSO-
PHY IN THE FACULTY OF PURE SCIENCE
OF COLUMBIA UNIVERSITY

BY

RAEMER REX RENSHAW, M.S.

NEW YORK CITY

1907



EASTON, PA. :
ESCHENBACH PRINTING COMPANY.
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TABLE OF CONTENTS.

Acknowledgment	4
Historical Introduction	5
Preparation and Properties of Certain Known Derivatives of 4-Aminophthalic Acid	6
Introduction	8
Dimethyl 4-aminophthalate	8
4-Aminophthalic Acid	10
Hydrochloride of 4-Aminophthalic Acid	13
Salts of 4-Aminophthalic Acid	14
4-Acetaminophthalic Anhydride	15
4-Aminophthalic Anhydride	16
4-Aminophthalamethylimide	16
4-Nitrophthalamethylimide	17
4-Aminophthalimide	18
Trimellitic Acid 4-Monoamide	19
Hydrochloride of Dimethyl 4-Aminophthalate	20
Action of Heat on Dimethyl 4-Aminophthalate	20
Acyl Derivatives of Dimethyl 4-Aminophthalate	21
Derivatives of the Acetic Acid Series	21
Dimethyl 4-Aminophthalate and Formic Acid	21
Dimethyl 4-Acetaminophthalate	21
Dimethyl 4-Propionaminophthalate	22
Dimethyl 4-isobutyraminophthalate	22
Dimethyl 4-Aminophthalate and Valeric Anhydride	22
Derivatives of the Benzoic Acid Series	23
Dimethyl 4-Benzoylaminophthalate	23
Dimethyl 4- <i>m</i> -Nitrobenzoylaminophthalate	23
Dimethyl 4- <i>p</i> -Nitrobenzoylaminophthalate	23
Derivatives of Carbonic Acid	23
Dimethyl 4-Urethanophthalate	23
Dimethyl 4-Phenyluraminophthalate	24
Tetramethyl Ester of 1,2,1',2'-Tetracarboxy- <i>sym</i> -diphenyl-urea	24
Derivatives of Dibasic Acids	25
Dimethyl Ethoxalyl 4-Aminophthalate	25
Dimethyl Oxalyl 4-Aminophthalate	26
Succinamic Acid of Dimethyl 4-Aminophthalate	26
Silver Succinamate of Dimethyl 4-Aminophthalate	26
Dimethyl 4-Succinimidophthalate	27
Phthalamic Acid of Dimethyl 4-Aminophthalate	27
Silver Phthalamate of Dimethyl 4-Aminophthalate	27
Dimethyl 4-Phthalimidophthalate	28
4-Aminophthalanil	28
Summary	28
Chronological Bibliography	30
Biographical	31

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R. R. R.

4-Aminophthalic Acid and Some of Its Derivatives.

Very little is to be found in the literature concerning 4-aminophthalic acid or its derivatives. The results of the early investigators were mostly negative. Due to this, and to the rather contradictory nature of such information as was found, as well as to the fact that an investigation on this subject would furnish a sequel to work previously done in this laboratory on the nitrophthalic acids, the research described in the following pages was undertaken.

As early as 1863, Muller¹ described an aminophthalic acid as a yellow crystalline substance, soluble in acids and bases. He obtained this from a nitro acid formed by nitrating phthalic acid. He does not give the methods of reduction.

Eight years later Faust² found that *m*-aminobenzoic acid was formed on reducing the nitro acid obtained by nitrating phthalic acid. He used tin and hydrochloric acid as a reducing agent. Baeyer,³ in 1873, confirmed Faust's² work, but he did obtain, however, the dimethyl ester of 4-aminophthalic acid by reducing the corresponding nitro compounds with zinc and hydrochloric acid. He had unknowingly separated out the 3-nitro ester before reducing.

None of these investigators recognized the fact that two isomeric nitrophthalic acids were obtained by nitrating phthalic acid, and from their descriptions it is evident that in their work on the acid itself they were dealing with the 3-nitro isomer.

Miller,^{4,5} who was the first to call attention to the two different nitro acids obtained by nitrating phthalic acid, has given the first authentic information regarding the 4-aminophthalic acid series. He found that he could reduce the 4-nitro acid with tin and hydrochloric acid, but that the resulting amino compound was so unstable that in attempting to de-tin the solution, carbon dioxide was split off and *m*-aminobenzoic acid resulted. He,

too, prepared the diethyl 4-aminophthalate by reducing the 4-nitrophthalate with alcoholic hydrochloric acid and zinc. He also obtained its acetyl derivatives. Edinger⁶, Onnertz⁷, and others have also prepared this ester.

In 1901, Seidel⁸ published an account of the preparation of 4-aminophthalic acid by the reducing of the 4-nitro acid with sodium sulphide. He described it briefly as a yellow voluminous substance crystallizing from alcohol and melting above 280°.

Hoesch⁹, in 1904, prepared the 4-aminophthalhydrazide both by the action of hydrazine hydrate on the diethyl 4-nitrophthalate at 130°, and by the reduction of the 4-nitrohydrazide with ammonium sulphide. He also prepared a number of its salts and derivatives.

A year later, Cohen and McCandlish,¹⁰ on reducing dimethyl 4-nitrophthalate with ammonium sulphide, obtained an impure product, which they thought contained a sulphurated compound.

Quite recently Wegscheider and Bondi¹¹ obtained the 4-aminophthalic acid 1-methyl ester by reducing the corresponding nitro compound with tin and hydrochloric acid, and by Baeyer's³ method with zinc and hydrochloric acid. They apparently found great difficulty in purifying the product, but finally by fractional crystallization the ester was obtained as a yellow not readily crystallizable substance, melting at 145°.

The following derivatives have been prepared either previous to, or during the process of this research.

Diethyl 4-aminophthalate has been prepared by Baeyer,³ Miller⁵ and others by the reduction of the 4-nitro-diethyl ester with zinc dust in an alcoholic hydrochloric acid solution. This ester was separated and purified in the same manner as the dimethyl ester described in the experimental part. From alcohol it crystallizes in prisms, melting at 95°. It is easily soluble in alcohol or ether, nearly insoluble in water. Its ethereal solution shows a faint blue fluorescence.

Diethyl 4-acetaminophthalate was obtained by Miller by the action of acetic anhydride on the ester. It crystallizes from

alcohol in microscopic leaves, melting at 123° . On long standing, acetic acid is given off.

Hoesch⁹ has described the following compounds:

4-Amino-phthalhydrazide was prepared by heating diethyl 4-nitrophthalate with an excess of hydrazine hydrate at $130-140^{\circ}$. The product crystallizes from water in microscopic yellow needles, melting above 305° . This amino hydrazide has, to a small degree, acid properties, dissolving in alkalies and reprecipitating again with carbon dioxide. It dissolves in hot dilute acids and reprecipitates, on cooling, acid-free. The hydrogen atom combined with the 1 nitrogen atom is replaceable by metals. Mineral acids at 150° in a bomb give *m*-aminobenzoic acid.

The hydrazide was obtained also from the 4-nitrohydrazide by reduction with ammonium sulphide.

Sodium-4-aminophthalhydrazide, prepared by treating the base with an aqueous solution containing the calculated amount of sodium, crystallizes with 7 molecules of water. It is moderately soluble in water, giving an alkaline reaction.

The *calcium*, *copper*, and a *copper basic salt* were obtained from this sodium salt.

1-Ethyl-4-aminophthalhydrazide was obtained by treating the sodium salt with ethyl iodide at $130-140^{\circ}$ in a bomb. It is somewhat soluble in boiling water from which it separates out in yellow flocks on cooling. These begin to melt at 155° .

1,4-Diacetyl-4-aminophthalhydrazide, obtained by boiling the hydrazide several hours with an excess of acetic anhydride, crystallizes from hot alcohol in small plates, melting at 212° . It is only slightly soluble in cold water. No experimental work for the determination of the position of the acetyl groups was mentioned.

1, 4-Diurethano-4-aminophthalhydrazide, obtained by heating the dry sodium salts with a calculated amount of ethyl chlorcarbonate, is precipitated from the alcoholic solution by the addition of water. The product begins to decompose at 100° and completely melts at $148-150^{\circ}$.

4-Aminophthalic Acid 1-Methyl Ester was obtained by Wegscheider and Bondi¹¹ after this dissertation had been started by reducing the 4-nitro acid ester with zinc or tin and hydro-

chloric acid. When zinc was used the solution was neutralized with sodium hydroxide, acidified with acetic acid and extracted with ether. The product was purified by dissolving in ammonia and fractionally precipitating with acetic acid. Melting point, 145° . It is easily soluble in alcohol and hot water, slightly soluble in cold water.

Most of the above work has been repeated and found to be substantially correct. Baeyer's³ diethyl ester and Hoesch's⁹ hydrazide were obtained.

The direct reduction experiments of Miller⁴ were repeated. It was found that 4-nitrophthalic acid can be reduced to the amino acid by tin and hydrochloric acid as Miller stated, and that carbon dioxide was evolved during the evaporations of a large excess of hydrochloric acid.

Seidel's⁸ sodium sulphide reduction was tried. This gave some amino acid, but the reduction was slow and the acid rather difficult to purify from some sulphurated compounds apparently formed.

The following pages include descriptions of the methods of preparation and properties of 4-aminophthalic acid, its salts, and some of the more simple derivatives, as well as a number of reactions of its dimethyl ester.

EXPERIMENTAL PART.

Since the 4-aminophthalic acid was usually prepared from its dimethyl ester, the latter compound will be described first.

Preparation of Dimethyl 4-Aminophthalate, $\text{H}_2\text{NC}_6\text{H}_3(\text{COO-CH}_3)_2$.—Phthalic anhydride was nitrated by the method described by Bogert and Boroschek¹² and the resulting 3- and 4-nitrophthalic acids rather thoroughly separated by fractional crystallization. Two hundred grams of the crude 4-nitrophthalic acid, dissolved in 320 grams of methyl alcohol, were boiled with reflux condenser for 8 hours with 60 grams of concentrated sulphuric acid, and the methyl alcohol evaporated. By this treatment the 4-nitrophthalic acid is nearly completely converted to the neutral ester, while the 3-nitrophthalic acid forms mainly the acid ester. The alcoholic solution of the mixed esters was poured into an excess of water, the oily layer

separated, and stirred up with a strong sodium carbonate solution. This dissolved the acid ester while the neutral ester remained as an insoluble white curd. It was filtered, washed and purified by recrystallization from alcohol.

The dimethyl 4-nitrophthalate thus obtained was reduced by Baeyer's³ method as follows: Fifty grams of the nitro ester were treated with 250 grams of alcohol and 500 grams concentrated hydrochloric acid. After cooling in ice water the mixture was stirred with a turbine and small amounts of zinc dust added from time to time. While it is not necessary to keep the solution cool during reduction, it was found that by doing so the product was less colored. It is also advisable to continue the addition of the zinc dust some time after the 4-nitro ester has completely dissolved, as otherwise intermediate reduction products may sometimes contaminate the amino ester. When the reduction is completed and the solution has become almost colorless, an equal volume of water is added, and the greater part of the acid neutralized by sodium hydroxide, the temperature being kept down by the addition of ice. Final neutralization is accomplished by the addition of sodium carbonate solution as long as the precipitate which is first formed redissolves on stirring. The amino ester is salted out with a saturated solution of sodium acetate, and the mixture allowed to stand in the refrigerator for a few hours. The amino ester crystallizes from the solution in slightly colored glistening scales. It is purified by recrystallizing from alcohol, or better, benzene. The yield on the nitro ester used was about 88 per cent. of the theory.

Dimethyl 4-aminophthalate crystallizes from alcohol or benzene in shining white plates; from water, in long hexagonal prisms. It melts at 84° (corr.). It is soluble in cold alcohol, acetone, chloroform, nitrobenzene, aniline, pyridine, or mineral acids; slightly soluble in hot water, carbon tetrachloride or ether; difficultly soluble in carbon disulphide or petroleum ether.

Calculated for $C_{10}H_{11}O_4N$: C, 57.40; H, 5.30; N, 6.70.
Found: C, 57.22; H, 5.26; N, 6.65.

PREPARATION OF 4-AMINOPHTHALIC ACID.

4-Aminophthalic acid was prepared by a number of methods:

1. By the saponification of dimethyl 4-aminophthalate: (a) with sodium ethylate; (b) with caustic alkalies.

2. By the reduction of the 4-nitrophthalimide and saponification of the resulting amino imide.

3. By the reduction of 4-nitrophthalic acid with stannous chloride and salting out the hydrochloride of 4-aminophthalic acid with concentrated hydrochloric acid.

4. By the reduction of the 4-nitro acid with sodium sulphide.

1. *Preparation from Dimethyl 4-Aminophthalate.*—(a) The sodium salt of the aminophthalic acid was prepared from the dimethyl ester as follows: An alcoholic solution containing 50 grams of ester was boiled for a half hour with a freshly prepared alcoholic solution of sodium ethylate made by dissolving 13 grams of sodium (calc. 11 grams) in alcohol. This slight excess of sodium was found to be desirable. From the mixture the sodium 4-aminophthalates separates out as a heavy yellow precipitate. It was filtered, washed with alcohol and dried. The salt thus prepared is practically pure. Yield: 53 grams. The acid was liberated from the sodium salt by the addition of the calculated amount of hydrochloric acid. If the solution is concentrated enough, the 4-aminophthalic acid immediately precipitates out as a heavy yellow granular powder, whereas, if the solution is sufficiently dilute the acid separates out only on standing in microscopic crystal crusts. Twenty grams of the sodium salt were dissolved in 200 cc. of water and the solution filtered. To this was added 43 cc. of hydrochloric acid (sp. gr. 1.1) containing 9.64 grams hydrogen chloride. The 4-amino acid came down immediately as a creamy granular powder.

(b) If sodium hydroxide is used for saponification, the ester is boiled with the calculated amount of the alkali for from 2 to 3 hours. The solution is filtered, and the acid precipitated with the calculated amount of hydrochloric acid. Yield: practically quantitative.

2. *Preparation from the 4-Nitro Imide.*—The 4-aminophthalimide is readily obtained from the nitro imide by reducing with

stannous chloride (for which, see below), and the resulting amino compound is easily hydrolyzed even by boiling down with concentrated ammonium hydroxide. From the hydrolyzed solution, the 4-amino acid is obtained by adding an amount of hydrochloric acid equivalent to the base used.

3. *Preparation by the Direct Reduction of the 4-Nitro Acid with Stannous Chloride.*—Miller⁴ has found that 4-nitrophthalic acid can be reduced with tin and hydrochloric acid, even at the temperature of the boiling water bath, without loss of CO₂. After concentrating and diluting, he precipitated the tin with hydrogen sulphide, filtered and again concentrated. From the solution, on cooling, crystals of the hydrochloride of *m*-aminobenzoic acid separated. On repeating this reduction at ordinary temperatures, the same results were obtained. It was also determined that the carbon dioxide was lost while evaporating off the excess of hydrochloric acid, but that the velocity of the decomposition was low.

An attempt was made to separate the hydrochloride of 4-aminophthalic acid without de-tinning. Three grams of 4-nitrophthalic acid were added to a solution of 12 grams of stannous chloride in 40 cc. of hydrochloric acid (sp. gr. 1.17) and the mixture allowed to stand. Practically complete solution resulted. After filtering, an equal volume of concentrated hydrochloric acid was added, and the solution refrigerated. The crystals separating gave considerable ash on ignition and were probably those of the tin double salt. On a further addition of hydrochloric acid and refrigerating, a crop of needle crystals were obtained. This was practically pure hydrochloride of 4-aminophthalic acid.

4. *Preparation by Direct Reduction of the 4-Nitro Acid with Sodium Sulphide.*—This is the principle Seidel⁸ used, but he did not describe the details of the method. Five grams of 4-nitrophthalic acid, 8 grams of sodium sulphide, 5 grams of sodium hydroxide, and 200 cc. of water were heated on a plate, the volume being kept at 100–200 cc. by the addition of water. A black precipitate of sulphur formed, and the color changed after long heating from wine to bottle-green. At the end of 15 hours, dilute sulphuric acid was added to acid reaction and the solution warmed, made neutral with potassium

hydroxide and filtered from sulphur. The calculated amount of hydrochloric acid (2.5 cc.) necessary to precipitate the amino acid if completely reduced was added. A white precipitate was obtained consisting practically entirely of sulphur, and hydrogen sulphide again evolved. The solution was warmed for some tin, filtered, more acid added, and allowed to evaporate spontaneously. The precipitate formed contained sulphur, potassium sulphate, 4-aminophthalic acid, and some unreduced 4-nitrophthalic acid. This method is workable but does not give the best results. It may be as Cohen and McCandlish¹¹ have suggested in the case of the ammonium sulphide reduction of the ester, that some sulphurated compound was formed, making difficult the separation and purification of the acid by this method.

4-Aminophthalic Acid, $\text{H}_2\text{NC}_6\text{H}_3(\text{COOH})_2$.—The acid obtained by the above methods was purified by extraction with water and alcohol, or by recrystallization from boiling alcohol, or, better, by boiling water to which a small amount of acetic acid had been added. From alcohol the acid comes down in a voluminous condition; from dilute acetic acid in microscopic crystal crusts. The voluminous variety is the more soluble.

4-Aminophthalic acid melts over a free flame with gas evolution, but immediately solidifies and finally carbonizes. When heated up to 320° in a melting point apparatus in both closed and open tubes, water is given off without melting. The resulting product does not then melt over a free flame before carbonizing. The acid is insoluble in boiling benzene, acetone, amyl alcohol, chloroform, carbon tetrachloride, carbon disulphide, nitrobenzene, benzaldehyde, ether, and naphtha. It is only slightly soluble in boiling water or 95 per cent. ethyl alcohol, very readily soluble in strong acids, and in alkalies with an evolution of heat. It is also soluble in warm aniline and pyridine.

On analysis the following figures were obtained:

	Calculated for. $\text{C}_8\text{H}_7\text{O}_4\text{N}$	Found.		
		1	2	3
Carbon.	53.01	52.67	52.86	52.97
Hydrogen.	3.89	4.02	3.87	3.16
Nitrogen.	7.75	7.96	7.54	7.88

In order further to prove the structure of this acid a number of transformations to substances previously described in the literature were carried out.

A small portion of the acid was boiled with aniline, a slight excess of acetic acid added, and the solution diluted. After standing for some time, long, thin needles separated, having the melting point (204° uncorr.) of 4-aminophthalanil. The anil had been prepared by the condensation of dimethyl 4-aminophthalate with aniline as described below. The formation of this product proved to be the easiest means of identifying the acid; it was used for such purposes throughout the research.

On diazotizing with an excess of hydrochloric acid, an acid was obtained melting at $150-151^{\circ}$ with an evolution of water. Claus and Dehne¹³ have obtained the 4-chlorophthalic acid, melting at 148° , by the oxidation of β -chlornaphthol. Miersch,¹¹ by the action of nitric acid on *p*-chlorhydrindone, obtained the same acid, melting at $150-150.5^{\circ}$.

The basicity was determined to be 2 by titration with standard alkali.

A considerable difficulty was experienced at first in esterifying the acid to the neutral ester from which it was obtained. As might have been expected of such strong methylating agents as dimethyl sulphate and methyl iodide, no positive results were obtained with them on the amino acids. Of all the methods tried, that of Bogojawlensky¹⁵ gave by far the best results. Two grams of the 4-amino acid were boiled with 5 grams of freshly fused sodium pyrosulphate and 50 cc. of absolute methyl alcohol for two hours in a reflux apparatus. The solution was filtered and the alcohol evaporated. A good crop of crystals resulted on diluting and cooling. They were recrystallized from benzene. M.P. $79-80^{\circ}$ (uncorr.). The ester melts at 84° (corr.).

Hydrochloride of 4-Aminophthalic Acid, $\text{HClH}_2\text{NC}_6\text{H}_3(\text{COOH})_2$.—The acid is dissolved in a small amount of very dilute warm hydrochloric acid and concentrated hydrochloric acid added. Practically all the amino acid can be precipitated as the hydrochloride by adding a large excess of the mineral acid. This hydrochloride separates out in cooling in yellow

needle clusters which gradually give up hydrogen chloride in contact with the air. On heating, decomposition occurs without melting. The hydrochloride is soluble in water or alcohol, insoluble in ether.

SALTS OF 4-AMINOPHTHALIC ACID.

Silver 4-Aminophthalate, $\text{H}_2\text{NC}_6\text{H}_3(\text{COOAg})_2$.—Two grams of the acid were dissolved in an excess of ammonium hydroxide, a solution containing 3.7 grams of silver nitrate added and the solution acidified with nitric acid. The silver salts separate as a cream colored curd resembling silver chloride. It is slightly soluble in hot water, and can be obtained in small thin plates by crystallizing from the solvent. It readily darkens in the air.

On ignition the following results were obtained: Calculated for $\text{C}_8\text{H}_5\text{O}_4\text{NAg}_2$: Ag, 54.64. Found: Ag, 54.5.

Barium 4-Aminophthalate, $\text{C}_8\text{H}_5\text{O}_4\text{NBa}$.—Barium 4-aminophthalate is precipitated from a solution of sodium 4-aminophthalate by the addition of a barium chloride solution. It comes down as a yellow not very soluble powder. It is somewhat soluble in boiling water. By using care, it can be obtained from this solvent in small thin flakes.

A determination of barium gave the following results: Calculated for $\text{C}_8\text{H}_5\text{O}_4\text{NBa}$: Ba, 42.43. Found: Ba, 42.79.

The copper, nickel, lead and calcium salts were precipitated by adding solutions of the corresponding cations to solutions of sodium 4-aminophthalate.

The copper salt first comes down as a but slightly soluble yellow-green, precipitate, which changes to deep green microscopic crystal nodules on standing in contact with water.

The nickel salt comes down as a dirty green somewhat soluble precipitate.

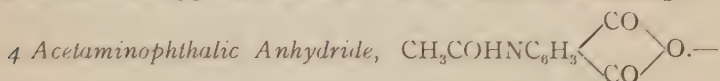
The lead salt is an amorphous yellow powder.

The calcium salt is precipitated from very concentrated solutions as yellow powder, but can be obtained by crystallizing from water in short, thick needles which readily darken in the air.

The potassium and *ammonium* salts are very soluble in water and could not be obtained in a crystalline form.

The *sodium* salt was obtained by the saponification of the ester with sodium methylate in alcoholic solution. The salt, insoluble in alcohol, separates out as a heavy cream colored precipitate. This was filtered and purified by recrystallization from aqueous alcohol. In general this product was obtained in small microscopic crystals, but at one time long, thin needles were obtained, which probably contained alcohol of crystallization. They decomposed immediately on filtering. Several unsuccessful attempts were made to get another crop of needles. Sodium 4-aminophthalate is very soluble in water, insoluble in alcohol. It darkens in the air if not dry.

4-Mercurichloraminophthalate.—A small amount of 4-amino-phthalic acid was dissolved in hydrochloric acid and a solution of mercuric nitrate and hydrochloric acid added. The solution was heated and allowed to stand. After some time thick needle clusters appeared which soon darkened on standing.

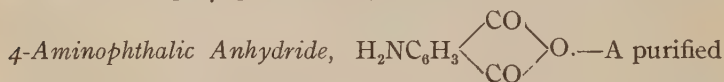


For the preparation of this compound five grams of the amino acid were boiled with an excess of acetic anhydride for from four to six hours, and the excess of anhydride evaporated. The product was stirred up with water, filtered, and washed twice with ether. After recrystallizing ten to twelve times from ethyl acetate to which acetic anhydride or acetyl chloride had been added, a product was finally obtained as small microscopic needles, melting at 206.7° (corr.). If the boiling with acetic anhydride is not continued so long, and the excess not boiled off, a product is obtained melting at 134° (uncorr.) with an evolution of water. This product gives off water extremely easily; even on drying in an air bath at $80\text{--}90^\circ$, it is changed almost wholly to the anhydride. This substance as well as the anhydride has to a very marked degree a tendency to give off acetic acid. In fact, it was almost impossible to obtain a product, which, after recrystallizing from ethyl acetate, would dissolve completely in that solvent. There was almost always a slight insoluble flocculent residue, particularly if the product had been standing in the air any length of time.

The anhydride is much more easily obtained by boiling the acid with acetyl chloride. After filtering and concentrating, white needles are obtained, which, by from two to three recrystallizations from the same solvent, give a constant melting point.

4-Acetaminophthalic anhydride is soluble in acetone, alcohol, ethyl acetate or amyl valerate, slightly soluble in ether. It is practically insoluble in benzene or petroleum ether.

A determination of nitrogen gives the following results: Calculated for $C_{10}H_7O_4N$: N, 6.84. Found: N, 6.82 and 6.88.



sample of the acid was heated in an air bath for two hours at $180-200^\circ$. It was then extracted with boiling water, boiling alcohol, and boiling ether, dried at 175° for an hour, re-extracted and dried at 110° . These precautions were taken because the samples previously prepared had given too low results, where one might have expected too high. It is fairly certain, however, that these low results were due to the impurities in the original acid. The anhydride does not melt but at a high temperature it gives off more water before carbonizing, probably due to the formation of the polymolecular imide. It is nearly insoluble in all the ordinary solvents.

On analysis the above sample gave the following results: Calculated for $C_8H_5O_3N$: N, 8.58. Found: N, 8.40 and 8.44.



compound was obtained in an attempt to prepare the 4-aminophthalimide by the action of aqueous ammonia on the dimethyl ester at higher temperatures. Five grams of the ester were heated with 20 cc. of strong ammonium hydroxide for 3 hours in a bomb at $180-190^\circ$. On cooling, long thin, canary-yellow needles were formed. The solution had an odor of methylamine. It was concentrated, cooled, and the crystals formed filtered. They were dissolved in hot, very dilute aqueous ammonia, bone-blackened, concentrated and refrigerated. After

several recrystallizations from the same solvent, a pure product was obtained melting at 242-243° (corr.).

Analysis for nitrogen gave the following figures: Calculated for $C_9H_8O_2N_2$: N, 15.95. Found: N, 16.06 and 16.09.

The 4-aminophthalmethylimide is very soluble in alcohol, acetone, or hot ethyl acetate; somewhat soluble in boiling water or benzene, and insoluble in petroleum ether. It sublimes under diminished pressure without much decomposition.

The following test was made to determine if the methyl group was on the imido or the amino nitrogen. One gram of the compound was distilled down twice with an excess of strong potassium hydroxide solution and the distillate passed through dilute acetic acid. An odor of methylamine was obtained from the acetic acid solution on the addition of potassium hydroxide. After cooling, the residue in a flask had nearly solidified. This was stirred up twice with warm absolute alcohol and the alcohol decanted. By this means most of the potassium hydroxide was removed. The potassium salt remaining was dissolved in water and the solution made slightly acid. On standing, an acid separated resembling 4-aminophthalic acid, and giving the 4-aminophthalanil on boiling with aniline.

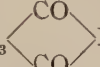
This product was also obtained by reducing the 4-nitro methylimide with stannous chloride and salting out the resulting aminoimide with hydrochloric acid. This hydrochloride separates in plates which are decomposed on treatment with water.

4-Nitrophthalmethylimide, $NO_2C_6H_3 \begin{array}{c} \diagup CO \diagdown \\ \diagdown CO \diagup \end{array} NCH_3$. —This was

prepared by heating the acid methylamine salt of 4-nitrophthalic acid at 175-180° in an air bath for two hours. On cooling, the melt solidifies to a yellow-brown crystalline mass. This was dissolved in 50 per cent. alcohol, bone-black and recrystallized several times from the same solvent. It is then obtained in nearly white long needles melting at 179-180° (corr.).

4-Nitrophthalmethylimide is very soluble in acetone, ethyl acetate or chloroform, much more soluble in hot alcohol than in cold, moderately soluble in benzene, ether, or boiling water.

Analysis for nitrogen gave the following figures: Calculated for $C_9H_6O_4N_2$: N, 13.63. Found: N, 13.67.

4-Aminophthalimide, $H_2NC_6H_3$  NH.—A number of dif-

ferent methods were tried in attempting to prepare this compound directly from the amino acid.

As above noted, the action of aqueous ammonia under pressure gave principally the methylated imide. Alcoholic ammonia, under pressure, gave a mixed product containing at least three different substances. One of these melted at about 200° (uncorr.), another at 238° (uncorr.), and a third at 293° (uncorr.). As the difference in solubility was too slight for an easy separation, the products were not obtained in amounts or in a sufficient state of purity for an analysis. It is probable, however, that there were formed the imide and the monomethylated and ethylated imides.

Both the acids and neutral ammonium salts of the acid were heated at different temperatures and extracted with acetone in various stages of the heating. As was expected, these procedures did not give an efficient means for the preparation. The temperature necessary for the formation of the imide, which was rather low, was sufficiently high for the substituted ammonia residue, that is, the aminophthalyl residue, to replace the ammonia residue of the imide. The acetone extract always contained besides small amounts of the imide other substances similar to those obtained by the partial decomposition of the ester by heat. By heating rapidly to 280 – 300° small amounts of yellow needle crystals of the imide were obtained.

When dry ammonia was passed over the anhydride, heated to 280 – 290° , a small amount of the imides sublimed.

At most only traces of the imide were obtained by heating an intimate mixture of the 4-aminophthalic acid and ammonium chloride.

The product sought, however, is very easily prepared by the reduction of the 4-nitroimide. Five grams of 4-nitrophthalimide, obtained by the action of heat on the 4-nitrophthalic acid ammonium salt were added to a solution of 20 grams of stan-

nous chloride, 150 cc. of hydrochloric acid, and 50 cc. of water. The solution was gently stirred with a turbine until all the nitroimide had dissolved and then twice the volume of the concentrated hydrochloric acid added. A cream colored precipitate immediately separated. The solution was allowed to cool and the hydrochloric acid decanted. The product was decomposed by shaking up with water, leaving a yellow residue. This, after several crystallizations from boiling water, gave long yellow needles, which began to sublime at 277° , gradually softened and finally melted to a dark brown liquid at 294° (corr.).

4-Aminophthalimide is nearly insoluble in petroleum ether, slightly soluble in cold water, ether, chloroform, and carbon disulphide. It is somewhat soluble in boiling water or benzene, very soluble in boiling alcohol or acetone.

On analysis the following was obtained: Calculated for $C_8H_6O_2N_2$: N, 17.33. Found: 17.48.

Trimellitic Acid 4-Monoamide, $H_2NOCC_6H_3(COOH)_2$.—This compound was obtained in an attempt to prepare the 4-cyanphthalic acid. While no particular endeavor was made to prevent hydrolysis, yet it is evident that such a hydrolysis does take place with extreme ease.

Four grams of 4-aminophthalic acid were dissolved in 8 cc. of hydrochloric acid and 5 cc. of water, the solution cooled, diazotized, and poured into a cuprous cyanide solution. After warming some time and filtering, the solution was repeatedly extracted with ether, the extracts united and evaporated. A number of procedures were used in working up this residue. Probably the best is the repeated precipitation from its ethereal solution by the addition of benzene. Ethyl acetate can be used instead of ether but less satisfactorily. By the careful addition of the benzene, microscopic crystal crusts can be obtained.

The product on saponification with potassium hydroxide gave off ammonia. From the ether extract of the solution after acidifying, a substance was obtained melting at $216-218^{\circ}$ with an evolution of water. Trimellitic acid melts at 216° .

Trimellitic acid 4-monoamide melts at 166° (corr.). It is

very soluble in alcohol, ethyl acetate and water, moderately soluble in amyl acetate and ether. It is practically insoluble in benzene, chloroform, or carbon tetrachloride.

On analysis the following figures for nitrogen were obtained: Calculated for $C_9H_7O_5N$: N, 6.7. Found: N, 6.6.

DERIVATIVES OF DIMETHYL 4-AMINOPHTHALATE.

Dimethyl 4-aminophthalate has been described (page 8). Before the above work on 4-aminophthalic acid had been performed, the following derivatives of its dimethyl ester were prepared:

Hydrochloride of Dimethyl 4-Aminophthalate, $HClH_2NC_6H_3(COOCH_3)_2$.—The amino ester was dissolved in dry benzene and treated with benzene saturated with dry hydrogen chloride. A gummy precipitate separated, which soon hardened to a crystalline mass. This was removed, washed with dry benzene and dried in a vacuum desiccator. It dissolved freely in water, but soon dissociates with precipitation of the free amino ester. In a moist atmosphere, it slowly gives off hydrogen chloride.

Action of Heat on Dimethyl 4-Aminophthalate.—The action of heat upon the dimethyl ester was rather interesting. When it is heated at 180° – 200° , methyl alcohol is split off and a slight odor of methylamine is obtained. If the heat is not continued very long, the residue is composed of substances differing but slightly in their solubilities, and having a wide range of melting points. On the other hand, if the heat is continued until no further decomposition takes place, a vitreous brown melt results. This is but very slightly soluble in any of the ordinary solvents, including strong boiling hydrochloric acid. It is soluble, however, in potassium hydroxide.

In the products analyzed, very pure ester was used. The melt was finely pulverized and repeatedly extracted with boiling water, alcohol, and ether. The highest percentage of nitrogen obtained was 9.09 per cent. The theory of the polymolecular imide is, nitrogen, 9.69 per cent. If, however, seven molecules condensed without the end molecular tying up, the product would give 9.08 per cent. nitrogen.

In view of the fact of the insolubility of the product in

hydrochloric acid, it is possible that the closed chain imido compound was formed, since here in contradistinction to the open chain compound, there would be no free amino group. The low analytical figures might well be explained on account of the inadequacy of the extraction method of purification.

ACYL DERIVATIVES OF DIMETHYL 4-AMINOPHTHALATE.

I. *Derivatives of the Acetic Acid Series.*

Dimethyl 4-Aminophthalate and Glacial Formic Acid.—Five grams of the amino ester were boiled for three hours with an excess of glacial formic acid. The excess of acid was then evaporated, and the residual oily material crystallized from alcoholic formic acid. In this way, a small amount of crystalline product was obtained. The mother-liquor appeared to contain one or two other substances, which, however, were not further investigated.

The substance, separated by crystallization from alcoholic formic acid, forms nearly colorless microscopic crystals, m. p. 179° (corr.), which are soluble in alcohol, hot ethyl acetate, acetone, or benzene; very difficultly soluble in ether, carbon disulphide, chloroform or petroleum ether. They are apparently quite easily hydrolyzed.

On analysis, the amount of nitrogen found was 6.66 per cent. This agrees closely with the theoretical amount of nitrogen present in the dimolecular condensation product, $(\text{CH}_3\text{OOC})_2\text{C}_6\text{H}_3\text{NHCH}:\text{NC}_6\text{H}_3(\text{COOCH}_3)_2$, resulting from a condensation of the formyl derivative first produced with a second molecule of the amino ester.

Nitrogen calculated for $(\text{CH}_3\text{OOC})_2\text{C}_6\text{H}_3\text{NHCOH}$, 5.92; nitrogen calculated for $(\text{CH}_3\text{OOC})_2\text{C}_6\text{H}_3\text{NHCH}:\text{NC}_6\text{H}_3(\text{COOCH}_3)_2$, 6.54; nitrogen found, 6.66.

Dimethyl 4-Acetaminophthalate, $\text{C}_6\text{H}_3(\text{COOCH}_3)_2\text{NHCOCH}_3$. Five grams of the amino ester were boiled for some time with an excess of acetic anhydride. The solution was then precipitated by dilution with water, the precipitate filtered out, washed thoroughly with water and crystallized from 30 per cent. alcohol. It was thus obtained in small, colorless crys-

talline plates, melting at 136.5° (corr.). It dissolves in alcohol, chloroform, benzene, acetone, hot carbon disulphide, ether, or water, but is very difficultly soluble in petroleum ether.

Calculated for $C_{12}H_{13}O_5N$: N, 5.58. Found: N, 5.76.

Dimethyl 4-Propionaminophthalate, $C_6H_3(COOCH_3)_2NHCO-C_2H_5$.—The amino ester was boiled with propionic anhydride, the propionic acid and excess of anhydride distilled off, the residual oil dissolved in alcohol, treated with bone-black, and precipitated by diluting with water and cooling in a freezing mixture. The substance was thus obtained in crystalline condition. It was recrystallized by dissolving it in benzene and carefully adding petroleum ether.

This propionyl derivative crystallizes in long, thin colorless needles, melting at 110.5° (corr.); soluble in alcohol, benzene, acetone, ethyl acetate, ether, or chloroform; insoluble in petroleum ether, or cold water.

Calculated for $C_{13}H_{15}O_5N$: N, 5.30. Found: N, 5.5 and 5.59.

Dimethyl 4-Isobutyraminophthalate, $C_6H_3(COOCH_3)_2NHCOCH(CH_3)_2$.—The amino ester was dissolved in just sufficient isobutyric anhydride to effect solution, and the solution was then boiled for an hour. On cooling, a brownish solid resulted. This was pulverized, washed with water, dissolved in alcohol, the solution treated with bone-black and cooled. The crystals which separated were purified by solution in benzene and reprecipitation with petroleum ether, or by recrystallization from dilute alcohol.

The isobutyryl derivative crystallizes in long, thin, colorless needles, melting at $122-123^{\circ}$ (corr.), which dissolve in benzene, chloroform, carbon disulphide, ether or acetone, but are very difficultly soluble in water or petroleum ether.

Calculated for $C_{14}H_{17}O_5N$: N, 5.0. Found: N, 5.16.

Condensation of the amino ester with valeric anhydride was brought about in the same manner as with isobutyric anhydride. The product was an oil, which refused to crystallize. It has much the same solubilities as the isobutyryl derivative. No analysis was made.

II. Derivatives of the Benzoic Acid Series

Dimethyl 4-Benzoylaminoththalate, $C_6H_5(COOCH_3)_2NHCO C_6H_5$.—The amino ester was dissolved in pyridine, the calculated amount of benzoyl chloride added, and the product precipitated by the addition of water. By crystallization from benzene, it was obtained in colorless needles, melting at $132-132.5^\circ$ (corr.); soluble in alcohol, benzene, acetone, chloroform, or ethyl acetate; slightly soluble in carbon disulphide; very difficultly soluble in ether, naphtha, or water.

Calculated for $C_{17}H_{15}O_5N$: N, 4.40. Found, N, 4.64.

Dimethyl 4-m-Nitrobenzoylaminoththalate, $C_6H_5(COOCH_3)_2NHCO C_6H_4NO_2(m)$.—The amino ester was dissolved in pyridine, treated with the calculated amount of *m*-nitrobenzoyl chloride and the mixture heated for some time. The mixture, when poured into water, separated an oil. This oil was washed free from pyridine hydrochloride, dissolved in alcohol, the solution concentrated to crystals, and the crystals recrystallized from benzene.

The substance forms nearly colorless scales, melting at 147° (corr.).

Calculated for $C_{17}H_{14}O_7N_2$: N, 7.83. Found: N, 7.87.

Dimethyl 4-p-Nitrobenzoylaminoththalate, $C_6H_5(COOCH_3)_2NHCO C_6H_4NO_2(p)$.—This was prepared in the same way as the meta derivative just mentioned. It crystallizes from alcohol in small yellowish flakes, melting at 202° (corr.). It is slightly soluble in cold alcohol, hot amyl acetate, or hot benzene; very difficultly soluble in carbon disulphide, chloroform or naphtha.

Calculated for $C_{17}H_{14}O_7N_2$: N, 7.83. Found: N, 7.95.

III. Derivatives of Carbonic Acid.

Dimethyl 4-Urethanophthalate, $C_6H_5(COOCH_3)_2NHCOOC_2H_5$.—Three grams of ethyl chlorcarbonate were added to a dilute alcoholic solution containing 4 grams of the amino ester and 2 grams of sodium carbonate. The reaction was accompanied by rise of temperature and evolution of carbon dioxide, and was completed by warming for a few minutes on the steam-bath. On careful dilution with water a precipitate was ob-

tained, which, recrystallized from boiling water, separated in long needles, melting at 122° (corr.).

This urethane is soluble in alcohol, acetone, ethyl acetate, ether, carbon tetrachloride, chloroform, or hot water; difficultly soluble in cold water, and apparently insoluble in petroleum ether.

Calculated for $C_{13}H_{15}O_6N$: N, 5.0. Found: N, 5.13.

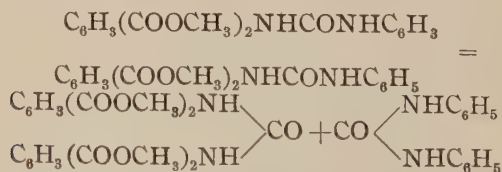
Attempts to prepare dimethyl 4-uraminophthalate by condensing the amino ester with cyanic acid as well as fusing with urea at various temperatures were unsuccessful.

Dimethyl 4-Phenyluraminophthalate, $C_6H_5(COOCH_3)_2NIICONHC_6H_5$.—Five grams of the amino ester, dissolved in dry benzene, were treated with excess of phenyl isocyanate, and the solution gently boiled for two hours. The benzene solution was then concentrated, petroleum ether carefully added, and the solution placed in an ice pack. The crystals thus obtained were purified by recrystallization from benzene.

The pure substance forms microscopic needles, melting at 138° (corr.), which are soluble in alcohol, benzene, ether, acetone ethyl acetate, or chloroform, but very difficultly soluble in carbon disulphide, or petroleum ether.

Calculated for $C_{17}H_{16}O_5N_2$: N, 8.50. Found: N, 8.64.

Tetramethyl Ester of 1,2,1',2'-Tetracarboxy-sym-diphenyl-urea, $C_6H_5(COOCH_3)_2NHCONHC_6H_5(COOCH_3)_2$.—It was thought from similar reactions of other phenyluramino compounds that dimethyl 4-phenyluraminophthalate might undergo the following decomposition on the application of heat:



Two grams of the phenyluramino compound were gradually heated. At 190° decomposition began and a slight odor of aniline was evolved. After heating for two hours with a gradual increase of temperature, the melt finally solidified at 222° to

a yellow-brown glass. In the meantime a few long needle crystals sublimed.

The melt was very slightly soluble in ethyl or amyl alcohol, acetone, acetic acid, aniline or aniline acetate; practically insoluble in boiling water, glycerine, ammonium hydroxide, or cold potassium hydroxide. It did not melt before burning over a free flame.

It seems then, that there was a more deep-seated reaction than the one expected. The explanation for this is probably to be found in the action of heat on the dimethyl 4-aminophthalate alone, as described above.

A successful attempt to prepare this compound was made, however, by the action of phosgene on the ester itself.

Four grams of dimethyl 4-aminophthalate were dissolved in pyridine and 4 cc. of a 20 per cent solution of phosgene in toluene added. A yellow precipitate was immediately formed with an evolution of heat. This dissolved, on shaking, to a cherry-red solution which finally turned yellow on heating. After boiling the liquid, it was poured into a large excess of water and the oil separating was washed, dissolved in alcohol, bone-blackened, the solution concentrated and refrigerated. In this way short needle crystals were obtained, which, after purification, melted at $213-14^{\circ}$ (corr.).

The tetramethyl ester of 1,2,1',2'-tetracarboxy-*sym*-diphenylurea is soluble in boiling water, alcohol or acetic acid; but only slightly soluble in hot benzene or chloroform.

Calculated for $C_{21}H_{20}O_8N_2$: N, 6.30. Found: N, 6.47.

IV. Derivatives of Bibasic Acids.

Dimethyl Ethoxalyl 4-aminophthalate, $C_6H_3(COOCH_3)_2NHCOCOOC_2H_5$.—Five grams of the amino ester were heated for several hours with a slight excess of ethyl oxalate. After distilling off the alcohol formed by the reaction, there remained an oil containing a small amount of a white precipitate. On extracting with boiling alcohol, the oil was all dissolved, while the precipitate remained insoluble. On concentrating the alcoholic extracts, the ethoxalyl derivative was precipitated, and it was then purified by recrystallization from alcohol.

As thus prepared, it formed small white flakes, melting at 126° (corr.); soluble in alcohol, benzene, acetone, ethyl acetate, ether, chloroform, or carbon tetrachloride; very difficultly soluble in naphtha.

Calculated for $C_{14}H_{15}O_7N$: N, 4.52. Found: N, 4.77 and 4.75.

Dimethyl Oxalyl-4-aminophthalate, $C_6H_3(COOCH_3)_2NHCOCO NHC_6H_3(COOCH_3)_2$.—The white insoluble precipitate observed in the foregoing reaction proved to be the corresponding oxalyl derivative resulting from the condensation of the ethoxalyl body with a second molecule of the amino ester. It was purified by digesting successively with alcohol, benzene, ether, and chloroform.

It is insoluble or very difficultly soluble in alcohol, benzene, ether, chloroform, acetone, ethyl acetate, carbon disulphide, nitrobenzene, petroleum ether, or water, and melts at 239° (corr.).

Calculated for $C_{22}H_{20}O_{10}N_2$: N, 5.9. Found: N, 5.68.

Attempts to prepare dimethyl 4-oxalimide phthalate by the action of heat on the ethoxalyl compound were made. The ethoxalyl derivative was, however, always recovered unchanged.

Succinamic Acid of Dimethyl 4-Aminophthalate, $C_6H_3(COOCH_3)_2NHCOCH_2CH_2COOH$.—This was prepared by boiling 2.5 grams succinic anhydride with 5 grams of the amino ester in benzene solution for some time. The succinamic derivative separated on concentrating the benzene solution and was purified by crystallization from water.

It crystallizes from water in colorless needles, melting at 173° (corr.), with loss of water and presumably with formation of the imide. It is soluble in boiling water, in alcohol, acetone, or ethyl acetate, slightly soluble in hot benzene, and very difficultly soluble in ether, chloroform, carbon tetrachloride, or naphtha.

Calculated for $C_{14}H_{15}O_7N$: N, 4.5. Found: N, 4.68 and 4.74.

Silver Succinamate of Dimethyl 4-Aminophthalate, $C_6H_3(COOCH_3)_2NHCOCH_2CH_2COOAg$.—By precipitating a solution of

the ammonium salt of the succinamic acid with silver nitrate, the silver salt generally separated in a gelatinous form, but on standing in the solution it gradually changed to a more granular condition. It was washed, dried, and ignited.

Calculated for $C_{14}H_{14}O_7NAg$: Ag, 25.94. Found: Ag, 26.06.

Dimethyl 4-Succinimidophthalate, $C_8H_3(COOCH_3)_2N(OC-CH_2)_2$.—Two grams of the succinamic acid were heated at $210-220^\circ$ in an oil bath for two hours. The resulting brownish melt was digested with a large excess of boiling water, the solution filtered, bone-blackened, and concentrated. Large needle crystals were formed, which after several recrystallizations gave a melting point of 153.4° (corr.).

The product is soluble in alcohol, benzene, chloroform, boiling water, or hot acetic acid; nearly insoluble in cold water or cold acetic acid.

Calculated for $C_{14}H_{13}O_6N$: N, 4.81. Found: N, 5.16 and 5.03.

Phthalamic Acid of Dimethyl 4-Aminophthalate, $C_8H_3(COOCH_3)_2NHCOC_6H_4COOH$.—A benzene solution of 5 grams of the amino ester was added to a saturated benzene solution of phthalic anhydride, and the whole boiled until it became decidedly turbid. On concentrating and cooling, microscopic crystals separated in large amount. These crystals were purified by dissolving in amyl acetate and adding petroleum ether, or better, by dissolving in alcohol and adding benzene. Attempts to crystallize from dilute alcohol resulted in more or less hydrolysis of the compound.

It is soluble in alcohol, acetone, or amyl acetate; slightly soluble in boiling benzene or in ether; very difficultly soluble in water, chloroform, or petroleum ether. It melts at about $166-167^\circ$ (corr.), with loss of water, passing thereby into the corresponding imide.

Calculated for $C_{18}H_{15}O_7N$: N, 3.93. Found: N, 3.92.

Silver Phthalamate of Dimethyl 4-Aminophthalate, $C_8H_3(COOCH_3)_2NHCOC_6H_4COOAg$.—This was prepared by adding silver nitrate to a neutral solution of the ammonium salt. It is precipitated as a curd, resembling silver chloride.

After thoroughly washing with water, it was dried and ignited.

Calculated for $C_{18}H_{14}O_7Na$: Ag, 23.22. Found: Ag, 23.10.

Dimethyl 4-Phthalimidophthalate, $C_6H_5(COOCH_3)_2N(OC)_2C_6H_4$.—The phthalamic acid was heated at 180-200° until the copious evolution of water which began at its melting point had ceased. The melt was dissolved in hot alcohol, bone-blackened and the solution concentrated. The phthalimido compound crystallizes from alcohol in long needle crystals, melting at 174° (corr.). It is soluble in benzene, chloroform, acetone, or hot alcohol; nearly insoluble in cold alcohol, in hot water carbon disulphide, ether, petroleum ether, acids or alkalis.

Calculated for $C_{18}H_{13}O_6N$: N, 4.1. Found: N, 4.25.

4-Aminophthalanil, $H_2NC_6H_3 \begin{array}{c} \diagup CO \\ \diagdown CO \end{array} NC_6H_5$.—Five grams of

dimethyl 4-aminophthalate were dissolved in boiling aniline, and the boiling continued for a short time. An excess of acetic acid was added to the cooled solution and then water. By this dilution the anil was thrown out as a yellow precipitate which was purified by crystallization from alcohol or from glacial acetic acid. As was indicated under the 4-amino acid, this anil can also be obtained by boiling the acid with aniline for a short time. The pure anil crystallizes in long, yellowish needles melting at 205.5° (corr.). It is soluble in alcohol, ethyl acetate, chloroform, or benzene, when hot; slightly soluble in hot water, or cold acetic acid; very difficultly soluble in acetone, ether, carbon disulphide, or naphtha.

Calculated for $C_{14}H_{10}O_2N_2$: N, 11.80. Found: N, 11.93.

SUMMARY.

1. 4-Aminophthalic acid can be readily prepared by the saponification of its imide or its dimethyl ester, as well as by the direct reduction of the 4-nitrophthalic acid with stannous chloride and salting out the hydrochloride of the resulting amino acid with concentrated hydrochloric acid.

2. The acid comports itself much like other aromatic dibasic

amino acid. It is stable toward alkalies, but boiling concentrated mineral acids slowly decompose it to the formation of *m*-aminobenzoic acid.

3. The acid and certain of its derivatives show a tendency to condense at higher temperatures to the polymolecular imido compounds.

4. The dimethyl ester reacts with ammonia to give a methylated imide rather than the hydrogen imide.

5. Acyl derivatives of dimethyl 4-aminophthalate are easily obtained by condensing the ester with acid anhydrides and chlorides. These substances are for the most part well-defined crystalline products.

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BIOGRAPHICAL.

The author of this dissertation entered the University of Oregon in September, 1898, receiving the degree of Bachelor of Science in 1902, and Master of Science in 1903.

During the year 1901-1902, he served as student assistant and scholar in the Department of Chemistry in the University of Oregon, and from 1902-1904 as Instructor in Chemistry at the same institution.

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He has published with M. T. Bogert an article on "Dimethyl 4-Aminophthalate and Certain of Its Acyl Derivatives," *J. Am. Chem. Soc.*, **28**, 617.

